UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/603,663	06/23/00	ZHU	L 25636-701

EXAMINER	
PRASTHOFER, T	
ART UNIT	PAPER NUMBER
1627	6

021971 HM12/0227
WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO CA 94304-1050

DATE MAILED: 02/27/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/603,663	ZHU ET AL.	
	Examiner	Art Unit	
	Thomas W Prasthofer	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2000 and 07 December 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *25-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☒ Claim(s) *14* is/are objected to.

8)☒ Claims *1-35* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

Detailed Action

Status of the Application

Receipt of a preliminary amendment and information disclosure statement on 09/25/00 and 12/07/00 are acknowledged.

Status of the Claims

Claims 1-35 are pending in this application. During a telephone conversation with Dr. Shirley Chen on February 7, 2001 a provisional election was made without traverse to prosecute the invention of Invention I, claims 1-24. Affirmation of this election must be made by applicant in replying to this Office action. Claims 25-35 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Election/Restriction

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-24, drawn to a method for selecting tester proteins capable of binding to a target peptide or protein, classified in class 435, subclass 7.1.

II. Claims 25-30, drawn to a method for selecting tester proteins capable of binding to a target peptide or protein, classified in class 453, subclass 7.1.

III. Claims 31-35, drawn to a kit, classified in class 435, subclass 320.1.

The inventions are distinct, each from the other because:

1. Inventions I and II are different and patentably distinct inventions. Inventions I and II are two different methods for selecting tester proteins capable of binding to a target peptide or protein because they include different and mutually exclusive method steps. For example,

Invention II includes arraying members of target expression vectors, clonal mating of yeast cells, and vectors containing human EST clones and Invention I does not. Invention I includes mating specifically between α and a type strains of yeast, lower limits to fusion protein diversity, expression of single-chain antibodies, and mutagenesis of isolated tester expression vectors and Invention II does not. Art anticipating or rendering obvious Invention I would not anticipate or render obvious Invention II. Each invention would support separate patents.

2. Inventions III and Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case Inventions I and II are each a method for selecting tester proteins capable of binding to a target peptide while Invention III is a composition, or kit, comprising yeast cells and yeast vectors that can be used in the processes of Inventions I and II. The kit of Invention III can be used for processes other than the methods of Inventions I and II. For example, the libraries can be used to screen for specific genes of interest using nucleic acid probes or antibodies without bringing the first and second libraries into contact within yeast cells.

3. Because these inventions are distinct for the reasons given above and

a. have acquired a separate status in the art as shown by their different classification ;

b. have different and separately burdensome: manual and/or computer: structure, name and bibliographical searches; and

c. have divergent subject matter, restriction for examination purposes as indicated is proper.

4. Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the

currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently filed petition under 37 CFR 1.48(b) and by the fee required under CFR 1.17(h).

Objections to the Claims

6. Claim 14 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 14 limits claim 16 which follows, rather than precedes, claim 14.

Claims Rejections - 35 U.S.C. 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claims 1-24 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility.

The instant specification discloses that the claimed method is useful for screening of "high-affinity binding pairs" and "for generating libraries of recombinant human antibodies and screening for their affinity binding with targets" e.g. see page 1, lines 20-23 .

Applicant's claimed method for selecting tester proteins capable of binding to a target peptide or protein must satisfy 35 USC 101 and 112 (1) as defined by the statute and case law.

In this regard, Applicant is directed to MPEP 2107; 2107.01 and 210.02 which provide guidelines for determining the criteria for satisfying utility and enablement.

Initially it is noted that merely disclosing the ability to make a compound or compounds (e.g. a library) is in itself insufficient utility to satisfy either 35 USC 101 or 112, first paragraph as determined by the U.S. Supreme Court. . Eg. See *Brenner v. Manson,* 383 U.S. 519, 148 USPQ 689 (1966).

According to the text of 35 USC sec. 101, an invention must be "useful". Our reviewing courts have applied the labels, "specific utility" (or "practical utility") to refer to this aspect of the "useful invention" requirement of sec. 101. (Nelson v. Bowler, 626 F.2d 853, 206 USPQ 881, 883 (CCPA 1980)). In Nelson, the court characterized "specific utility" (or "practical utility") as "a shorthand way of attributing real-world value to claimed subject matter. In other words, one skilled in the art can use a claimed discovery in a manner which provides some immediate benefit to the public." (Id. at 856.)

With respect to the issue of pharmaceutical utility and vague assertions of biological activity applicant is further directed to *In re Kirk* , 376 F.2d 936, 941, 153 USPQ 48, 52 (CCPA 1967)) and *Cross v. Iizuka* , 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985), wherein the Federal Circuit labeled applicant's assertion of "biological activity" without more specifics as a "nebulous" expression. Such statements, the court held, "convey little explicit indication regarding the utility of a compound" and do not satisfy either the utility and/or the enablement statutory requirements.

The claimed method for selecting tester proteins capable of binding to a target peptide or protein, is not supported by a specific asserted utility and does not, without further research and experimentation, provide an immediate benefit to the public.

Rather, the claimed method encompasses screening any peptide or polypeptide for its ability to bind to any other peptide or polypeptide. Since many thousands of such interactions are known to occur, it certain that interactions between polypeptides will identified using the claimed method. This does not provide an immediate benefit to the public, however, because the disclosure does not provide any means or guidance for distinguishing interactions of potential utility from those with no utility. Any benefit to the public (to one of ordinary skill in the art) is speculative.

Thus, the determination of utility is to take place at some future time, only when the properties of the selected test and/or target proteins have been elucidated. Absent a disclosure of those properties, the asserted utility screening for "high-affinity binding pairs" and "for generating libraries of recombinant human antibodies and screening for their affinity binding with targets" lacks specificity. Note, because the claimed invention is not supported by a specific asserted utility for the reasons just set forth, credibility cannot be assessed.

This is not to say that inventions that are to be used exclusively in a research setting (i.e., research tools) always lack a specific asserted utility.

Indeed, many research tools such as telescopes, gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility. (See USPTO Utility Guidelines, page 12.)

However, inventions that have a specifically identified utility must be distinguished from those whose utility requires further research to identify or reasonably confirm. (Id.) Research tools (such as gas chromatographs, screening assays, etc.) are useful in the sense that they can be used in conjunction with other method steps to evaluate materials other than themselves or to arrive at some result.

In the absence of an asserted specific utility, the "useful" requirement may be established by reference to a well established utility. A "well established utility" is a "specific utility" which is well known, immediately apparent and implied by the specification based on the disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art.

The method claimed is not supported by a well established utility, however, because neither the specification as filed nor any art of record discloses or suggests any property or activity for the affinity binding pairs to be selected such that another non-asserted utility would be well established for these combinations of molecules.

Claims Rejections - 35 U.S.C. 112, 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-24 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims Rejections - 35 U.S.C. 112, 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 2 and 4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims refer to "a first transcription sequence encoding etc." and to "a first nucleotide sequence encoding etc." This language may imply that there is a difference between a "transcription sequence" and a "nucleotide sequence" as used in the claims. It is not

clear, however, that there is a difference between a transcription sequence and a nucleotide sequence if they both encode polypeptides.

10. Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim recites a "target fusion protein" in lines 1 and 15 and a "target sequence encoding the target protein or peptide" in line 14. The terms "target fusion protein" and "target protein or peptide" do not have equivalent meaning but appear to be used as equivalent terms in the claim. If Applicant intends the meaning of the two terms to be identical, the Examiner suggests changing the claim to use one of the terms consistently. If Applicant does not intend the meaning of the two terms to be identical, the Examiner suggests the two terms to be identical, Applicant is required to make the differences clear in the language of the claim.

11. Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim recites a "target fusion protein" in lines 18 and a "target sequence encoding the target protein or peptide" in line 9. The terms "target fusion protein" and "target protein or peptide" do not have equivalent meaning but appear to be used as equivalent terms in the claim. If Applicant intends the meaning of the two terms to be identical, the Examiner suggests changing the claim to use one of the terms consistently. If Applicant does not intend the meaning of the two terms to be identical, Applicant is required to make the differences clear in the language of the claim.

12. Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Neither the claims nor the specification provide a definition of what it means for "libraries of precursor sequences" to be "specifically designed for the target peptide or protein." One using the claimed invention would not be able to determine the metes and bounds of the claimed invention.

13. Claims 10-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 10-12 recite the limitation "target peptide or protein." There is insufficient antecedent basis for this limitation in the claim. Claim 1 recites "target fusion protein."

14. Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "derived from" is vague and indefinite because the neither the claims nor the specification provide a definition of or a means of determining whether a polypeptide sequence is "derived from" another. Through mutagenesis one might generate any number of sequences that may include portions of sequence homology with other proteins.

15. Claims 11 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "proteins that are known to bind to the target peptide or

protein" is vague and indefinite. It is not clear, for example, if the phrase means proteins for which: a) target binding has been documented in the literature, b) one using the method knows bind the target, or c) only a small number of people know bind the target.

16. Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 13 recites the limitation "first nucleotide sequence" in line 14. There is insufficient antecedent basis for this limitation in the claim.

17. Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 13 recites the limitation "second nucleotide sequence" in line 15. There is insufficient antecedent basis for this limitation in the claim.

18. Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 14 recites the limitation "first nucleotide sequence" in line 17. There is insufficient antecedent basis for this limitation in the claim.

19. Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as

the invention. Claim 14 recites the limitation "second nucleotide sequence" in line 19. There is insufficient antecedent basis for this limitation in the claim.

20. Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "substantially conserved" in claim 15 is a relative term which renders the claim indefinite. The term " substantially conserved " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The relative conformations between the first and second polypeptide subunits has been rendered indefinite.

21. Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "mimics" in claim 16 is a relative term which renders the claim indefinite. The term " mimics " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. In the context of the claim, "mimics" is used in the art to indicate similarity in function or structure. One structure mimics another similar structure to a degree but, without further qualification, the degree of structural similarity between molecules in order to say that one structure "mimics" the other is a matter of judgement and not definite.

22. Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 18 recites the limitation "tester expression vector" in line 8. There is insufficient antecedent basis for this limitation in the claim.

23. Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 18 recites the limitation "the selected clones" in line 8. There is insufficient antecedent basis for this limitation in the claim.

24. Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 18 recites the limitation "the first and second nucleotide sequences" in line 9. There is insufficient antecedent basis for this limitation in the claim.

25. Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 18 recites the limitation "the isolated tester expression vectors" in lines 9-10. There is insufficient antecedent basis for this limitation in the claim.

Claims Rejections - 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

26. Claims 1- 4, 10-17, 20, 21, and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Hoeffler and Russell (1999, WO 99/28502).

This reference is a method of screening a DNA construct libraries encoding single chain fragments of immunoglobulin variable domains (page 15, lines 18-24). The method includes a target fusion protein comprising the DNA binding domain (DBD) of a transcription factor fused to a target peptide (page 16, line 9 – page17, line 3) and a tester fusion protein comprised of a single chain antibody library fused to the activation domain of a transcription factor (page 17, lines 5-8 and figure 1). The method includes using a yeast expression system including a reporter gene (page 18, lines 8-14) including mated haploid yeast cells (page 22, lines 21-25). The preceding citations anticipate current claims 1-4.

Embodiments of the single chain fusion reagents, including those anticipating current claims 14-17 are found on page 23. Transcriptional activators included but are not limited to GAL4, GCN4, ADR1 (page 28, lines 16-20) and LacZ (page 30, lines 14-19), anticipating claim 24. Page 30, lines 10-12 discloses screening for unknown antibodies that interact with a target of interest, anticipating current claim 11. Current claims 10 and 12 are anticipated as well because no mutagenesis is involved and independently derived precursor sequences for the

subunits of single chain antibody libraries is inherent in the process of making the libraries because the two subunits are derived from separate PCR reactions (pages 32-34). Page 37, lines 12-24 and page 38, lines 7-9 disclose the use of antigens associated with a disease state including tumor surface antigens, anticipating current claims 20 and 21.

Claims Rejections - 35 U.S.C. 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

27. Claims 1-12, 20, and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nandabalan et al. (May, 2000, filed June 13, 1997) U.S. Patent No. 6,057,101 and Hoeffler and Russell (1999, WO 99/28502).

The Nandabalan reference teaches methods for detecting protein-protein interactions that include expressing a library of tester fusion proteins and a target fusion protein in yeast cells and selecting those yeast cells in which a reporter gene is expressed, see, for example, "SUMMARY OF THE INVENTION" columns 4 and 5 (reads on the corresponding method steps of claim 1). The reference also teaches the expression of chimeric genes that are not specifically designed for the target protein, see, for example, column 9, line 34 through column 10, line 23.

The Nandabalan reference teaches transforming the library of tester expression vectors into yeast cells which contain a reporter construct, see, for example, "SUMMARY OF THE INVENTION" columns 4 and 5 (reads on the corresponding method step of current claim 2). The 1st and 2nd transcription sequences encoding the activation and DNA binding domains of a transcription activator read on the corresponding domains in current claims 2 and 3.

Columns 4 and 5 also teach a tester fusion protein vector comprising sequences that encode one domain of the transcription activator and a tester protein, a target fusion protein vector comprising sequences that encode one domain of the transcription activator and a target protein, a 1st population of haploid yeast cells containing a library of tester expression vectors, and a 2nd population of haploid yeast cells containing a target expression vector (reads on current claim 4). The same sections also teach mating of haploid yeast cells of opposite mating types and $\underline{\alpha}$ and $\underline{a}$ type strains of yeast (reads on current claims 5 and 6).

The Nandabalan reference also teaches the diversity of fusion proteins is at least $1x10^6$, $1x10^{10}$, and $1x10^{12}$ in claims 38-41 (reads on current claims 7-9). If the diversity of each of the two libraries is at least 50,000, the total diversity is at least $2.5x10^9$.

Column 9, line 34 through column 10, line 23 teaches the expression of chimeric genes that are not specifically designed for the target protein, the expression of chimeric genes are not derived from one or more proteins that are known to bind the target protein, and the diversities of the chimeric genes are not generated by mutagenesis (reads on current claims 10-12).

Figure 6 and column 9, lines 34-43 of the reference teach target fusion proteins associated with disease states including cancer (reads on current claim 20). According to figure 3 and column 17, lines 45-55, the reporter gene is selected from a group including but not limited

to β-galacosidase, chloramphenicol acetyl transferase (CAT), luciferase, or green fluorescence protein (reads on current claim 24).

The Nandabalan reference does not explicitly teach libraries containing two independently varying subunits fused with a transcriptional regulator

However, Hoeffler and Russell teach the expression of two-subunit fusion protein libraries in which the sequences are joined by a linker sequence and the sequence of each subunit varies within the library independently of the other subunit and heavy-chain and light chain variable regions.

It would have been obvious to anyone of ordinary skill in the art at the time that the invention was made to use the two-hybrid assay system of Nandabalan et al. with the single chain antibody expression library of Hoeffler and Russell. Motivation for this combination is found in the Hoeffler and Russell reference on pages 1-4 and 37-43. The screening of single chain antibodies in the two-hybrid expression system allows the rapid identification of antibody-antigen pairs. This motivation extends to the screening of any two-subunit proteins, such as receptors and transcription factors in which altering the combinations of subunits produces molecules with different functions.

28. Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Thomas W. Prasthofer** whose telephone number is **(703) 308-4548**. The examiner can normally be reached on Monday-Friday, 8:00-4:30.

29. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat can be reached on (703) 308-2439. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-2742.

30. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Thomas Prasthofer, Ph.D.

2/26/01

BENNETT CELSA
PRIMARY EXAMINER